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16. ABSTRACT

Radon progeny attached to environmental aerosols have characteristic activity median diameters between 0.1 and 0.3 μm. A comparison of experimental and theoretical particle deposition patterns in human lungs has revealed certain systematic inconsistencies among measured and predicted distributions within this range of particle sizes. It is the objective of this focused note to address the potential significance of these apparent discrepancies and comment how current lung dosimetry and risk estimates for inhaled radon progeny would be affected.

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SCIENTIFIC NOTE

BRONCHIAL DEPOSITION OF INHALED PARTICLES: DOSIMETRY IMPLICATIONS FOR RADON PROGENY

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Abstract — Inconsistencies exist between experimental inhalation exposure data and theoretical models predicting tracheobronchial aerosol deposition in human subjects. The relevance of these anomalies affecting radon progeny dosimetry are discussed regarding enhanced deposition and reduced mucociliary clearance at bronchial bifurcations, and relevance of unattached fractions.

INTRODUCTION

Radon progeny attached to environmental aerosols have characteristic activity median diameters between 0.1 and 0.3 μm[1,2]. A comparison of experimental and theoretical particle deposition patterns in human lungs has revealed certain systematic inconsistencies among measured and predicted distributions within this range of particle sizes. It is the objective of this paper to address the potential significance of these apparent discrepancies and comment on how current lung dosimetry and risk estimates for inhaled radon progeny would be affected.

AEROSOL DEPOSITION IN HUMAN BRONCHIAL AIRWAYS

Experimental data

An extensive, systematic series of aerosol deposition experiments with human test subject volunteers has been performed at the laboratory of the Gesellschaft für Strahlen und Umweltforschung (GSF), Frankfurt, FRG. The data are currently used by the International Commission on Radiological Protection (ICRP) Task Group on Respiratory Tract Dosimetric Models for analyses of factors affecting the behaviour of inhaled particulates. Therefore, this data will be considered here. The Frankfurt GSF results, reviewed by Heyder[3] and Stahlhofen[4], show that within the accuracy of the experimental procedure (approximately ± 2%) no deposition has been detected within the tracheobronchial region for particles as large as 2 μm in aerodynamic diameter, and down to 0.08 μm in geometric size. Their summarised data on bronchial deposition for different controlled breathing protocols and inhaled particulate diameters are compiled in Table 1.

Theoretical predictions

With the use of an aerosol deposition model developed specifically for the inhalation of short-lived radon progeny[5,6], we have calculated tracheobronchial deposition patterns for particulate diameters in the 0.05 – 1.0 μm size range. This spectrum is characteristic for a lognormal activity size distribution with activity median diameters (AMDs) between 0.1 and 0.3 μm, and geometric standard deviations between 2 and 3. In order to facilitate comparison with the experimental data, we selected two of the three breathing patterns shown in Table 1 which represent the typical breathing parameters for rest and moderate activity, with respiratory minute volumes of 7.5 $l.min^{-1}$ (250 $cm^3.s^{-1}$ flow rate, 4 s breathing cycle) and 22.5 $l.min^{-1}$ (750 $cm^3.s^{-1}$ flow rate, 4 s breathing cycle) respectively. The third breathing pattern with a respiratory minute volume of 15 $l.min^{-1}$ (500 $cm^3.s^{-1}$ flow rate, 4 s breathing cycle) is usually assumed to characterise domestic exposure to adults[6,7]. A second deposition model, developed specifically to study the influence of hygroscopicity on aerosol deposition[8], was also used to calculate bronchial

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deposition for the above aerosols. In our calculations we assumed equal inspiration and expiration times without pause, consistent with the experimental breathing pattern. Results of these calculations for monodisperse particles are presented in Figure 1. Although using different morphometries and deposition equations, there is excellent agreement between the two models. Thus, from a theoretical perspective, deposition fractions from 2 to 10% may have been anticipated for particles between 0.1 – 0.3 μm, inconsistent with the experimental evidence from the Frankfurt GSF experiments.

The predictions of a theoretical model will, obviously, be affected by the assumptions made in its derivation. Here, we shall comment briefly on deposition patterns calculated using other models which, although based upon differing assumptions, give results which are in accord and consistent with our findings. Recently Ferron *et al*[9] calculated bronchial deposition for different morphometric lung models, deposition equations, and computational methods, for the same breathing patterns as shown in Table 1, and for three particulate diameters. The mean and the range of deposition fractions for nine different combinations are compared with our results in Figure 1, indicating good agreement. For 0.08 and 0.5 μm particles bronchial deposition ranges from 1 – 15%, dependent on model assumptions. While Ferron *et al* note that total deposition data are in good agreement with the experimental data, calculated bronchial deposition values are in general larger than the corresponding experimental data. Similar results have been found by Yu and Diu[10] who compared different morphometric geometries, using similar deposition equations, though a different computational method. In other investigations, various deposition calculations have been performed specifically for radon progeny attached to submicron particles; Jacobi and Eisfeld[7] reported deposition fractions of 6 and 4% for 0.1 and 0.25 μm AMD particles, respectively, while the corresponding deposition fractions obtained by James and Birchall[11] were 4 and 3%. From a comparison between the Frankfurt GSF experimental data and theoretical predictions, it may be concluded that the deposition models apparently consistently over-estimate particulate deposition in human bronchial airways.

It should be noted here that inhaled radon progeny under environmental conditions are attached to particles of polydisperse aerosols. The size distribution of these particles is usually approximated by a lognormal distribution, characterised by an activity median diameter (AMD) and a geometric standard deviation (σ_g). The latter clearly affects particulate deposition;

Table 1. Tracheobronchial deposition patterns of unit density spheres for mouth (M) and nose (N) breathing as a function of particulate size and breathing parameters.

Particulate diameter (μm)	Deposition fraction					
	250 $cm^3.s^{-1}$ flow rate 8 s breathing cycle		250 $cm^3.s^{-1}$ flow rate 4 s breathing cycle		750 $cm^3.s^{-1}$ flow rate 4 s breathing cycle	
	M	N	M	N	M	N
0.08	–	*	–	*	–	*
0.10	–	*	–	*	–	*
0.20	–	–	–	–	–	–
0.40	–	–	–	–	–	–
0.70	–	–	–	–	–	–
1.00	–	–	–	–	–	–
2.00	–	–	0.01	–	0.01	–
3.00	0.03	–	0.04	0.02	0.05	0.02
4.00	0.07	0.03	0.07	0.03	0.11	0.03
5.00	0.14	0.05	0.11	0.04	0.17	0.03
6.00	0.18	0.06	0.15	0.05	0.20	0.02
7.00	0.22	0.05	0.18	0.05	0.22	0.01
8.00	0.23	0.03	0.18	0.04	0.21	–
9.00	0.22	0.02	0.18	0.02	0.17	–
10.00	0.22	–	0.17	0.01	0.14	–
12.00	0.18	–	0.12	–	0.09	–
15.00	0.11	*	0.08	*	*	*

– Indicates zero deposition.
* No data available.

deposition for a polydisperse aerosol with an AMD between 0.1 and 0.3 μm and σ_g = 2.5 is about a factor of 2-3 higher than for monodisperse particles in the same size range[5].

DISCUSSION

The clinically observed site selectivity[12,13] of bronchial tumours may be related to the regional deposition pattern of inhaled radon progeny within the tracheobronchial tree. While calculations from various mathematical models predict deposition fractions in the bronchial region of the order of some per cent, the experimental data of the Frankfurt GSF laboratory indicate no deposition at all in the size range characteristic of radon progeny aerosols. If there actually is no deposition in bronchial airways, which reasons can we then advance to explain the finding that current dosimetry models cannot be so incorrect, for a comparison with epidemiological information shows reasonable agreement between the dosimetric and the epidemiological approach for lung cancer risk assessment[14]? Here, we will discuss the radiological implications of this apparent contradiction between theoretical predictions and experimental observations for the dosimetry of airborne radon progeny.

In contrast to the Frankfurt GSF findings, tracheobronchial deposition *in vivo* has been observed for particles down to about 0.1 μm in tests using spontaneous breathing protocols conducted at the New York University Medical Center (NYUMC)[15,16] (a comparison of theoretical predictions with the NYUMC tracheobronchial deposition data has been presented elsewhere[17]). Several reasons have been advanced[4,16] in efforts to explain differences between the two experimental data sets, such as: possible hygroscopic growth of inhaled particles, the role of controlled versus spontaneous breathing during exposures, and different interpretations of particulate clearance mechanisms in bronchial and pulmonary airways. The issues are yet to be resolved and it is beyond the scope of this note to address them. Here, we accept the experimental findings as published. It is worthwhile, however, to comment that in both protocols, deposition is not measured directly but is inferred from clearance measurements – which requires making assumptions regarding compartmental clearance as a function of time. Regarding this issue and the identification of short-term clearance with tracheobronchial clearance, Smaldone *et al*[18] have recently written ". . . the activity remaining in the lung at 24 hrs reflects much more than deposition in terminal airways and alveoli".

Since experimental bronchial deposition hinges upon the identification of the fast clearance phase with mucociliary clearance, the existence of a slow clearance phase in the tracheobronchial tree could account for the discrepancy. If such a slow clearance phase does exist, then Stahlhofen[4] has concluded ". . . that a determination of regional deposition based on clearance measurements would generally under-estimate tracheobronchial deposition and over-estimate alveolar deposition".

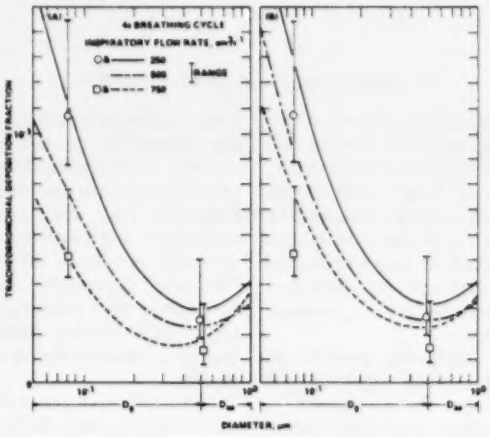

Figure 1. Theoretically predicted regional aerosol deposition patterns in man for monodisperse particles. Panel A curves calculated using the Hofmann model[6]; Panel B curves calculated using the Martonen *et al* model[8]. Both sets of curves are compared to the mean and range of theoretical deposition data presented by Ferron *et al*[9]. D_g and D_{ae} are geometric and aerodynamic diameter, respectively.

Reduced clearance at airway bifurcations has been described qualitatively by Hilding[19] for bronchial airways down to the 6th generation of bronchi. Quantitative information has been provided by Gore and Patrick[20] and Svartengren *et al*[21] for the tracheal-main bronchial junction in rabbits and rats, respectively, clearly indicating a slow clearance phase. At bifurcation sites the mucus blanket splits into two parts, sometimes leading to a whirlpool at the carinal ridge[19]. Hilding has also supposed that squamous islands devoid of cilia occur preferentially at such sites. Both effects lead to a retardation of mucus flow or to actual stasis in the centre of the carinal ridge where ; ision takes place. Mucociliary clearance rates may be further reduced by cigarette smoke which has been shown to temporarily inhibit clearance action, particularly at bifurcations[22].

For short-lived radon progeny initially deposited at airway bifurcations or subsequently transported there from distal locations, a prolonged residence time at bronchial bifurcations of the order of only a

few hours would allow all nuclides to decay at the site. This would increase the radiation dose to this region relative to regions with normal mucus flow. Also, it may be argued that if 24 hours is considered to be the time within which all particles deposited in the bronchial tree are cleared by mucociliary action, then such a prolonged retention in upper bronchial airways would not be detected in clearance measurements. It would, however, be long enough to increase local radiation doses.

Enhanced deposition of submicron particles at bronchial bifurcations has been reported by Schlesinger *et al*[23], Schlesinger and Lippmann[24], and Cohen *et al*[25] for human tracheobronchial replica casts, and by Martin and Jacobi[26] and Martonen *et al*[27] for tracheobronchial airway models. These measurements showed (i) that aerosol deposition was enhanced at bronchial bifurcations relative to downstream tubular airway segments, and (ii) that deposition within bifurcation zones *per se* was heterogeneous, exhibiting highly concentrated deposits at carinal ridges. Preferential deposition at airstream dividers may be partially attributed to localised flow instabilities and secondary flows.

Such enhanced deposition at upper bronchial bifurcations would not be reflected in tracheobronchial deposition measurements: For 0.28 μm particles, inhaled at a flow rate of 15 l.min^{-1}, theory would predict a tracheobronchial deposition of 3.37%[6]. If we take published enhancement factors for the first four bronchial bifurcations[23] for this particle size and flow rate, and assume that enhanced deposition at bifurcation sites is only effective during inspiration (corresponding to the aforementioned measurement), then tracheobronchial deposition will be 3.57%. Such a minute difference cannot be detected against the experimental error of the measurement and the inter-subject variability of particle deposition, irrespective of the deposition data used in our comparison.

Because of the combined effect of enhanced deposition and impaired clearance at bifurcation sites, epithelial cells located within bifurcation zones, and specifically at carinal ridges, receive much higher doses than along tubular airway segments. A detailed description of these calculations is presented elsewhere[28]. Results of these calculations reveal that doses at upper bronchial bifurcations are (on the average) about a factor of 5 higher than current dose estimates which are based on a uniform nuclide distribution on bronchial airway surfaces. While the dose distribution at bifurcations in upper bronchial airways is determined by the initial deposition pattern and by airway clearance kinetics, the dose distribution at bifurcations in peripheral air passages is most likely affected by the clearance mode. From this discussion on the deposition and clearance patterns at bronchial bifurcations we infer that if *total* bronchial deposition is – in accordance with the Frankfurt GSF data utilised by the ICRP (and henceforth addressed here) – actually smaller than currently predicted by theoretical models, then enhanced deposition and reduced clearance at *bifurcation sites* (leading to increased exposure to target cells located there) may offset a reduced hazard evaluation based upon the presumed deficit in dose.

If deposition of attached radon progeny is actually much smaller, then the unattached fraction of ^{218}Po atoms, f_A, becomes very significant. Theoretical models predict that unattached atoms of about 0.001 μm diameter are deposited very efficiently in upper bronchial airways by random Brownian motion because of their high diffusion coefficient[6]. Unfortunately, for ultrafine particles, we have no experimental information regarding dispersion of deposited materials among airways, for experimental data to date have been reported for total deposition only[29,30,31]. Deposition of unattached atoms in the tracheobronchial region is about a factor of 10-20 higher than for the attached fraction. Thus a value of 5-10% for f_A would give roughly the same dose as for the attached ^{218}Po fraction. Since deposition of free atoms peaks in upper bronchial generations, the ratio between free and attached particle deposition is even higher there than for total tracheobronchial deposition.

If the dose to epithelial cells is averaged over the entire thickness of the bronchial epithelium, then the dose delivered by ^{218}Po alpha particles in upper bronchial airways is slightly smaller than the dose contribution by ^{214}Po alpha particles. Thus, an unattached fraction f_A of about 10% would account for about one third of the total dose. Such a conclusion is consistent with the finding of James[32] who has suggested that for an unattached fraction f_A of about 15%, both unattached and attached radon progeny produce approximately the same mean bronchial dose. In lobar and segmental bronchi the dose averaged over the whole epithelial thickness is about a factor of 2-3 higher than the basal cell dose which has been used in previous[6,7,34,32] dose calculations. If we, therefore, assume that the dose contribution from attached radionuclides is negligible compared to free atoms (because of no deposition), then an unattached fraction f_A between 10 and 15% would yield roughly the same dose as has been predicted in previous dose calculations for basal cells.

Dependence of lung cancer incidence on the unattached fraction of radon progeny has been reported by Cross *et al*[33], who indicated that tumourigenic efficiency increased concomitant with

an increase in the unattachment fraction. Therefore, it appears that the potential importance of these unattached particles should be reconsidered in future dose assessments. The change in the philosophy[13,28,32] to calculate doses to secretory cells, uniformly distributed throughout the bronchial epithelium, rather than to the deep lying basal cells increases the significance of unattached nuclides.

CONCLUSION

A comparison between the Frankfurt GSF laboratory's data base and several predictive aerosol deposition models has made it apparent that current models over-estimate the reported values of particle deposition in bronchial airways. Use of the experimental data for risk assessment and hazard evaluation of airborne radionuclides would, therefore, give relatively lower estimates of bronchial dose. But, bronchial deposition patterns may be very heterogeneous, with bifurcation zones being sites of preferential accumulation of inhaled particulates. Such 'hot spots' cannot, to date, be detected with the instrumentation and protocols used in the inhalation exposure studies with human subjects. Dosimetric considerations presented here; namely, (i) enhanced deposition, (ii) impaired clearance, and (iii) a reappraisal of the role of unattached nuclides on lung dosimetry, could offset a supposedly lessened deficit in airway cell dose implied by the aforementioned Frankfurt GSF data. It is interesting to note that these factors (i.e., (i)-(iii)) would increase the dose specifically in upper bronchial airways where the majority of tumours has been observed[13].

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